UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,077	05/08/2007	Yoshio Miki	08178.0031	3057

7590 12/02/2010

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER
1300 I STREET, N.W.
WASHINGTON, DC 20005

EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
12/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,077	MIKI ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This action is responsive to the Response to Supplementary Species Election Requirement filed September 10, 2010, as well as the Amendments and Reply of June 17, 2010, in which claims 1, 4-6, 10-12, and 14-15 were amended. As noted below in paragraph 4, claims 1 and 4-9 are now under consideration. Claims 2-3 and 10-16 remain withdrawn. Applicant's amendments and arguments have been thoroughly reviewed, and are persuasive in part. Particularly, applicant's amendments and arguments have overcome the rejection of claim 1 under 35 USC 102(b) as being anticipated by the dbSNP entry for rs2277559, as the prior art does not disclose assessing a genotype of a subject as required by claim 1 as presently amended. Applicant's amendments have also overcome the rejections under 35 USC 112, second paragraph, set forth in the prior Office action. However, applicant's amendments and arguments are not persuasive with regard to the rejection of the claims for lack of enablement under 35 USC 112, first paragraph, for the reasons set forth below. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The new Oath/Declaration filed June 17, 2010 has been accepted. The amendments to the specification filed June 17, 2010 have been entered and overcome the objection set forth in the prior Office action.

Election/Restrictions

4. Applicant's supplemental election of the "genetic polymorphism at the 11th nucleotide of the sequence defined by SEQ ID NO: 4 in CYP2C* gene" in the reply filed on September 10, 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The examiner concurs that claims 1 and 4-9 read on the elected species, and those claims as directed to the elected species are now under consideration herein.

5. Claims 2-3 and 10-16 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and non-elected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 28, 2009.

Priority and Requirement for Information

6. Receipt is acknowledged of the certified translation of applicants' foreign priority document (filed June 17, 2010). As the translation establishes that the invention under consideration herein was disclosed in applicant's foreign priority document filed November 5, 2003, the examiner concurs with applicant's argument that the Requirement for Information mailed with the Office action of February 19, 2010 is unnecessary. Accordingly, the **Requirement is withdrawn**, and no further response thereto is required.

Claim Rejections - 35 USC § 112, second paragraph

7. Claims 1 and 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS' AMENDMENTS:

Claims 1 and 6-7 are indefinite because it is unclear how the practice of the claimed method actually achieves "predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy" as set forth in the preamble of claim 1. Claim 1 as amended recites a final step of "assessing a genotype(s) of said one or more genetic polymorphisms to thereby predict the risk of the occurrence of granulocytopenia caused by paclitaxel therapy". The language "to thereby predict the risk…" does not make clear how the assessment of the genotype actually relates to risk (in contrast with, e.g., dependent claims 4-5 and 8-9, which specify the manner in which genotype and risk actually relate). Accordingly, the manner in which the methods of claims 1 and 6-7 actually function is not made clear by the language of these claims.

Claims 6-7 are indefinite because it is unclear how the claims relate to and further limit claim 1, from which they depend. Claim 1 as amended is drawn to a method "for predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy" in which a genetic polymorphism is identified and comprising a final step of "assessing a genotype(s) of said one or more genetic polymorphisms to thereby predict the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in

said subject". Claim 6 is drawn to the "method of claim 1" further comprising identifying (in a "gene isolated from the subject") one or more genetic polymorphisms including the elected "genetic polymorphism at the 11th nucleotide of the sequence defined by SEQ ID NO: 4 in CYP2C8 gene". It is not clear how the identifying of claim 6 actually relates to the method of claim 1 and to the "assessing a genotype" of polymorphisms and "predicting" of risk required thereby. Claim 6 as written appears unrelated to the method of claim 1, as there is no indication as to how the polymorphism identified in claim 6 relates to the "assessing" and "predicting" of claim 1 (and it is noted that the "assessing" specifies use of "said one or more genetic polymorphisms", suggesting that the additional polymorphism(s) of claim 6 are also involved in the "assessing" step in some way). Accordingly, clarification is required with regard to how claim 6 relates to claim 1. Claim 7 is included in this rejection because it fails to provide any further clarification with regard to the relationship between the SEQ ID NO: 4 polymorphism and assessing or predicting risk. (Dependent claims 8-9 are not included in this rejection because those claims do clearly indicate how the genotype defined by SEQ ID NO: 4 relates to risk prediction).

Claim Rejections - 35 USC § 112, first paragraph

8. Claims 1 and 4-5 remain rejected, and claims 6-9 are now rejected, under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is noted that applicant's amendments

necessitating the rejoinder of claim 6-9 also **necessitated the inclusion of claim 6-9 in this rejection.** The rejection is on essentially the same grounds set forth in the prior Office action of February 19, 2010 (see the rejection of record). Regarding applicant's claim amendments, it is noted that independent claim 1 has been amended to include a new final step of "assessing a genotype(s) of said one or more genetic polymorphisms to thereby predict the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in said subject". While this amendment clarifies that the claimed invention requires an assessment of genotype that relates (in some way) to risk determination, the claims continue to lack enablement for the same reasons set forth in the prior Office action. It is noted that the intended use of "predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in a subject" was considered and addressed in the prior action, and that the same rationale for rejection pertains to claims requiring the new "assessing" step, as such claims also require a reliable association between genotype and granulocytopenia risk. With regard to claims 6-9 (newly considered herein), those claims require the additional genotyping of "a genetic polymorphism at the 11^{th} nucleotide of the sequence defined by SEQ ID NO: 4 in CYP2C8 gene". However, as was discussed in the prior Office action, applicant's data (obtained using a group of only 54 patients) and conclusion that "the potential for the occurrence of granulocytopenia can be reliably predicted by using" the elected SNP combination of claims 6-9 would be recognized by one of skill in the relevant art an identification of a possible association requiring further study. While the specification does report a statistically significant association between both elected SNPs and

granulocytopenia risk, a study of this type and limited scope would not be considered sufficiently reliable to enable a method that actually requires prediction of risk in a patient, for all the reasons set forth in the prior Office action (see in particular pages 8-10). It is additionally noted that the prior art does not teach an association between the elected SNP combination of claims 6-9 and risk of granulocytopenia caused by paclitaxel therapy. Thus, the prior art does not provide any further guidance or evidence that supports a conclusion that the claimed invention is enabled.

9. **The response traverses the rejection on the following grounds**.

First, the reply argues that the enablement requirement of 35 USC 112, first paragraph requires that the specification "describe how to make and use the invention" (citing MPEP 2164), and quotes from pages 22 and 24 of the specification, asserting that the specification "provides more than sufficient disclosure regarding how to use the invention". The response notes that the basis of the rejection thus appears to be not a lack of enablement but a "lack of credible utility". The reply references case law cited in the MPEP with regard to this utility requirement, noting that a utility may be considered credible even if the invention has not been proved "to a clinical certainty". Next, the reply argues that 'the clinical data in this invention is impressive," citing the disclosure of "statistically significant, strong correlations between CYP2C8/BUB1b genes and granulocytopenia," and noting examples from the specification of small p values and high odds ratios (at pages 31, Tables 12-13). Regarding the Ioannidis and Dahlman references cited in the rejection, the reply argues that "the 'large studies' described in those references exhibited much higher p values and/or much lower odds ratios than

the study in the present disclosure" (again referencing Tables 12-13) as compared to Ioannidis and Dahlman. The reply thus concludes that "even though the patient population studied in the present disclosure was much smaller that those of the large studies, the sample size was sufficient to demonstrate statistically more significant and stronger genetic associations than the large studies described in the references". The reply also notes that the cited references pertain to genetic associations for complex diseases as compared to the claimed invention, which "concerns granulocytopenia caused by paclitaxel therapy". Finally, the reply notes that the failure of the dbSNP database to disclose risk associations with the elected polymorphism(s) "only supports the novelty and non-obviousness of the claimed invention" and does not "in any way undermine the utility of the claimed invention".

These arguments have been thoroughly considered but are not persuasive. First, it is noted that the issue of lack of credible utility has not in fact been raised. The utility of the invention, when evaluated in accordance with the guidance provided in MPEP 2107, is in fact considered credible in view of the preliminary data reported in the specification and the plausible basis for a possible functional relationship between BUB1b and the function of paclitaxel (as discussed at, e.g., pages 16-17 of the specification). In order for the utility of the invention to be considered non-credible, the asserted utility must be based on "seriously flawed" logic or facts inconsistent with such logic, etc. (see MPEP 2107.02 III); such is not the case here. However, as noted in MPEP 2164.07, the fact that applicant has provided a specific and substantial utility that is credible "does not provide a basis for concluding that the claims comply with all the

requirements of 35 USC 112, first paragraph". Rather, to satisfy the enablement requirement, one skilled in the art must be able to practice the claimed invention without undue experimentation. Applicant's claims require "predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in a subject". The present rejection does not question the enablement of various methods of determining a genotype or detecting polymorphisms, etc. (such as sequencing, TaqMan, etc., as cited in the reply). Rather, the issue is whether such methods may actually be performed to achieve the prediction of the risk of occurrence of granulocytopenia caused by paclitaxel therapy. The claims do not simply require the performance of steps of detecting polymorphisms to achieve, e.g., genotyping (which methods are clearly enabled by both the specification and the art). Rather, the present claims require that the genotype of a subject may be used to predict risk. As noted in the rejection, it is unpredictable based on the guidance in the specification and in the art as to whether this is in fact the case. As already indicated on the record, the data in the specification appears preliminary in nature, relying on data obtained using an extremely small group of subjects, and the results have not been replicated (as one skilled in the art would require before concluding that a particular genotype may actually be relied upon in predicting a risk associated with a particular therapy). Applicant's arguments pertaining to the cited Ioannidis and Dahlman references are also non-persuasive. These references in fact support the Office's conclusion that small studies (such as that reported in the specification) are particularly prone to support "statistically significant" associations that are not found to be truly significant upon further, more rigorous study; note, e.g., the

statement by Ioannidis et al that “Typically, large studies and subsequent research suggested weak associations or no associations at all, compared with strong associations proposed by smaller studies and first research” (page 570, right column). Further, these references make clear that one of skill in the relevant art at the time of applicant’s invention would not have reached a conclusion regarding the validity of an association based on one small study in the absence of replication (regardless of the p-values and/or odds ratios reported); note again the teaching of Ioannidis et al that “only 16% of genetic associations identified were subsequently replicated with formal statistical significance, without heterogeneity or bias” (page 570, left column), and Dahlman’s teaching that their results "emphasize the need for large datasets, small P values and independent replication if results are to be reliable” (abstract). With regard to applicant’s statements about the complexity of the conditions addressed in the Ioannidis et al and Dahlman references as compared to granulocytopenia caused by paclitaxel therapy, applicant provides no evidence or specific arguments supporting a conclusion that granulocytopenia is less complex than the conditions addressed by Ioannidis et al and Dahlman. Further, the specification acknowledges at page 16 that the “SNPs found by the present invention are though to be related to granulocytopenia by a yet unknown mechanism". Thus, these arguments cannot be considered persuasive. Finally, with regard to the dbSNP database entries cited in the prior Office action, it is noted that these prior art teachings are considered relevant to the enablement of the invention simply because one of skill in the art may, in some instances, rely upon the teachings of the prior art to provide that which is lacking in the

application itself. However, in the present case, the closest prior art reference (i.e., the cited dbSNP entries), do not support enablement of the method claimed, which requires predicting granulocytopenia risk.

This rejection is maintained.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 8:30 am-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571/272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634